Received: 22 June 2022 | Revised: 6 October 2022 | Accepted: 13 October 2022

DOI: 10.1002/dta.3391

RESEARCH ARTICLE

WILEY

Drug testing for mitragynine and kratom: Analytical challenges and medico-legal considerations

Anders Helander[1,2] | **Alexia Rylski**[2]

[1]Department of Laboratory Medicine, Karolinska Institute, Stockholm, Sweden

[2]Department of Clinical Pharmacology, Karolinska University Hospital, Stockholm, Sweden

Correspondence
Anders Helander, Karolinska University Hospital Huddinge, C1:74, SE-141 86 Stockholm, Sweden.
Email: anders.helander@ki.se

Abstract

Mitragyna speciosa, known as kratom, is a tropical tree native to Southeast Asia that has long been used to increase energy and in traditional medicine. Kratom leaves contain several indole alkaloids including mitragynine, mitraciliatine, speciogynine, and speciociliatine, which have the same molecular formula and connectivity, but different spatial arrangements (i.e., diastereomers). A routine liquid-chromatographic–high-resolution mass-spectrometric (LC-HRMS) multi-analyte method for addictive and herbal drugs in urine did not separate mitragynine from speciogynine and speciociliatine. Separation and individual measurement of the four diastereomers was possible with an improved LC method. All diastereomers were detected in 29 patient urine samples who tested positive for mitragynine with the routine method, albeit at variable absolute amounts and relative proportions. The presence of all diastereomers rather than individual substances indicated that they originated from the intake of kratom (i.e., plant material). Speciociliatine dominated in most samples (66%), whereas mitragynine and mitraciliatine were the highest in 17% each. A kratom product (powdered plant material) marketed in Sweden contained all diastereomers with mitragynine showing the highest level. In Sweden, there are signs of an increasing use of kratom in society, based on the results from drug testing, the number of poisons center consultations on intoxications, and customs seizure statistics. Because there may be health risks associated with kratom use, including dependence, serious adverse reactions, and death, analytical methods should be able to identify and quantify all diastereomers. In Sweden, this is important from a legal perspective, as only mitragynine is classified, whereas the other three diastereomers, and kratom (plant material), are not.

KEYWORDS
diastereomers, drug testing, kratom, mitragynine, urine

1 | INTRODUCTION

Plants within the genus *Mitragyna* have been used for hundreds of years to increase energy and reduce fatigue and in traditional medicine to treat a wide spectrum of ailments.[1] *Mitragyna speciosa*, commonly known as kratom, is a tropical tree native to Southeast Asia that contains several indole alkaloids, of which mitragynine and its potent metabolite 7-hydroxymitragynine are the most investigated.[2,3] Kratom leaves produce mild stimulant effects at low doses, whereas moderate-to-high doses exhibit opioid-like analgesic and sedative effects.[4,5] The leaves may be chewed as they are, brewed into a tea, or processed as powder. However, despite therapeutic potentials in pain management,[6] possessing limited opioid adverse effects (e.g., respiratory depression) and milder withdrawal symptoms compared with morphine-like opioids, controlled research studies are lacking, and there are no approved medical uses of kratom.[7–10]

Over the past decades, use of kratom as a recreational drug and self-medication herbal supplement has spread also in the Western world,[9,11] with indications of further rises during the opioid crisis and COVID-19 pandemic.[12] People are using kratom, typically in powder, capsule, or liquid form, as a substitute for illicit and prescription drugs, or to manage opioid withdrawal symptoms, acute and chronic pain, and mental health problems, or as an energy and mood booster possibly linked to activity at serotonin receptors.[13] Nevertheless, there are safety concerns related to the use of kratom.[14] Large doses have been reported to cause acute serious adverse effects (e.g., seizures and cardiovascular effects)[15,16] and long-term use severe liver injury.[17,18] Deaths attributed to kratom alone, or as a contributing cause, have been reported.[19–21]

Targeting the opioid receptor system, chronic frequent kratom use may lead to the development of tolerance, dependence, and withdrawal symptoms, indicating a need for control measures.[8] The regulation of kratom and mitragynine varies around the world and between countries in the EU.[22] In the United States, efforts to make kratom a scheduled drug at the federal level have failed, but there are bans in some states and warnings have been issued.[8] In Sweden, mitragynine was classified as a narcotic substance in 2011, whereas kratom (i.e., crude plant materials), despite containing mitragynine, is legal to possess but not to consume, process, or pack in portion doses. Hence, kratom is sold on several websites but officially for the production of soap, thereby mimicking the misleading marketing of new psychoactive substances (NPS, "Internet drugs") as bath salts and plant fertilizers.[23]

Another ambiguity is that the Swedish drug classification uses the stereo-specific definition of mitragynine (i.e., methyl(E)-2-[(**2*S*,3*S*,12b*S***)-3-ethyl-8-methoxy-1,2,3,4,6,7,12,12*b*-octa-hydroindole [2,3-a]quinolizin-2-yl]-3-methoxyprop-2-enoate). However, besides mitragynine, three other compounds with the same molecular formula and connectivity, but different spatial arrangements at carbon-3, carbon-15, and carbon-20 (i.e., diastereomers), are present in kratom: mitraciliatine, speciogynine, and speciociliatine (Figure 1). Because only one of the four diastereomers in kratom is covered by the Swedish drug classification, this fact risks complicating the interpretation of analytical results and legal prosecution.

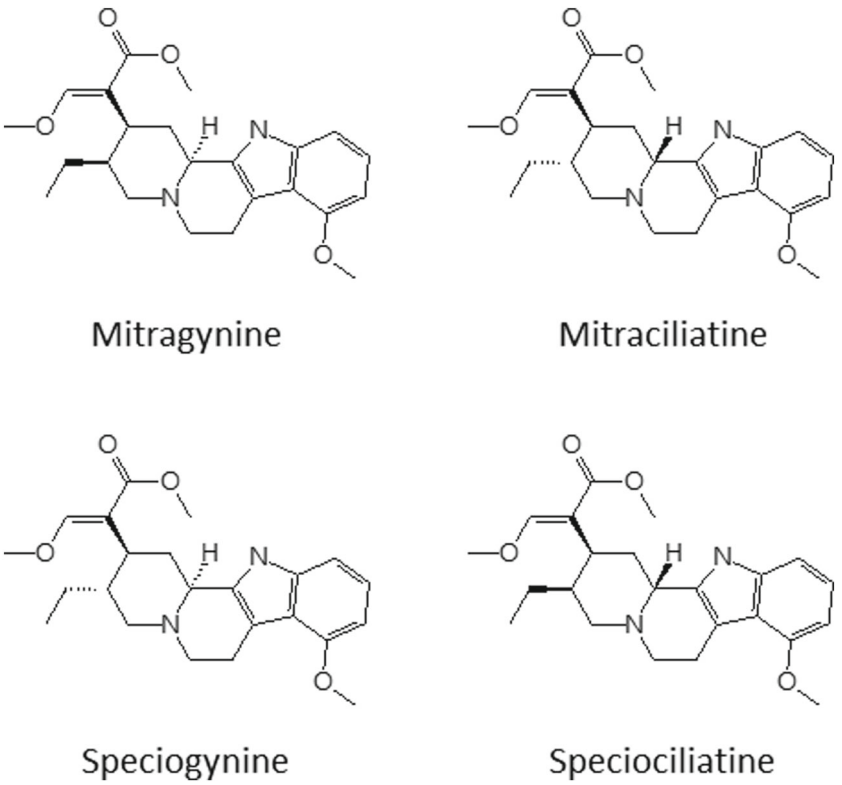

FIGURE 1 The chemical structures of mitragynine and its three diastereomers that occur in the plant *Mitragyna speciosa*. The diastereomers differ in the configurational positioning at carbon-3, carbon-15, and carbon-20 (mitragynine: *SSS*; speciogynine: *SSR*; speciociliatine: *RSS*; and mitraciliatine: *RSR*). Absolute configuration: *R* = rectus (right) and *S* = sinister (left).

The present work was undertaken to study the appearance of mitragynine and its diastereomers in urine samples submitted for drug testing.

2 | METHODS

2.1 | Materials and clinical samples

A certified reference material of mitragynine was obtained from Chiron AS (Trondheim, Norway), and speciociliatine and speciogynine were from Cayman Chemical Co. (Ann Arbor, MI, USA). Mitraciliatine was a kind gift from Dr. T. Arndt (Germany).[24]

The patient urine samples ($N = 29$) used for this study were de-identified surplus volumes of consecutive samples submitted for drug testing to the Karolinska University Laboratory in Huddinge (Stockholm, Sweden) and that tested positive for mitragynine with a cutoff of 100 μg/L (there is no nationally harmonized cutoff). They were collected consecutively from September 2021 until March 2022 and were first stored in a refrigerator for 2–3 weeks and then frozen at −20°C, conditions where the substances are considered stable for

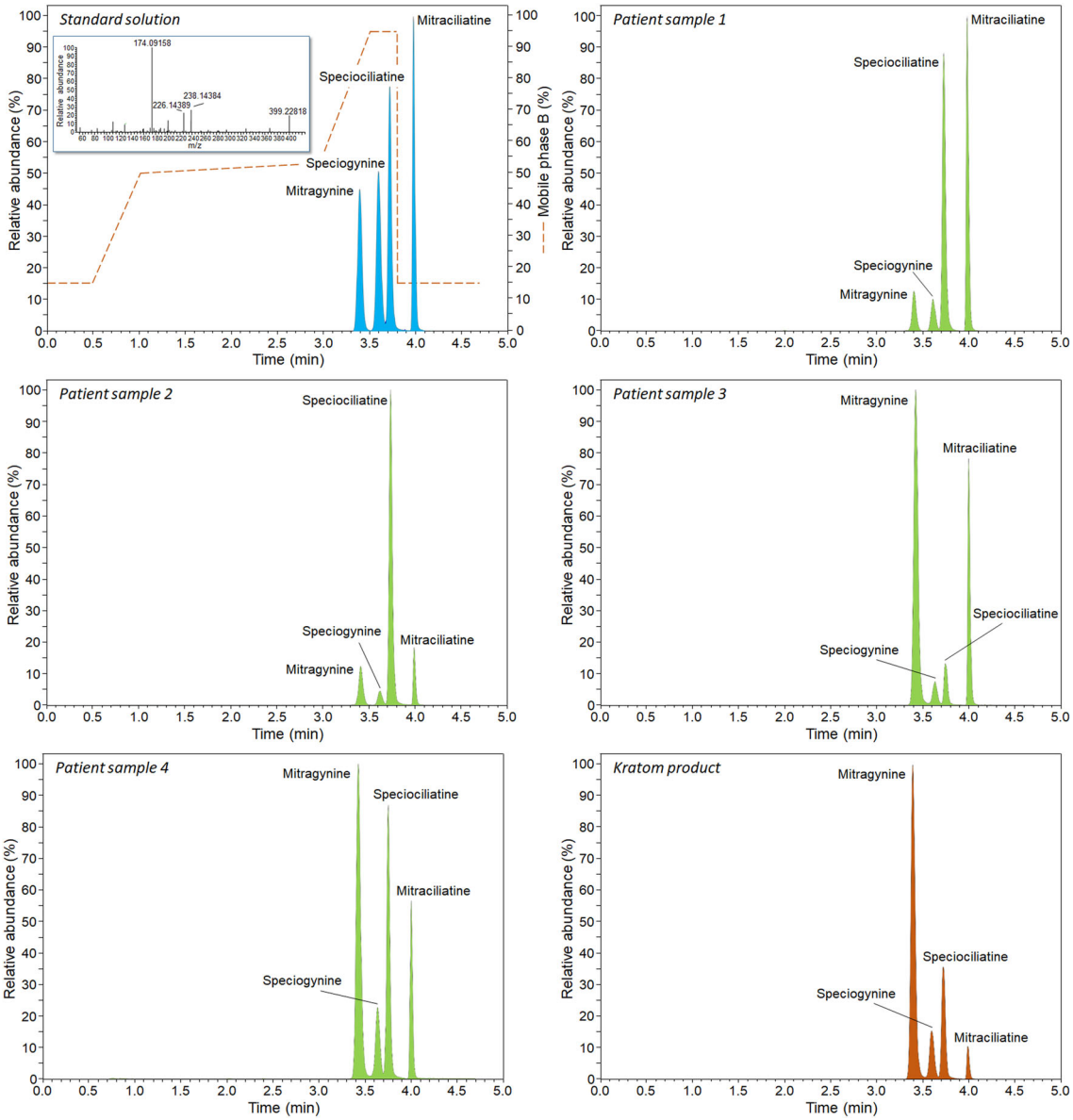

FIGURE 2 Analytical results obtained with the gradient (shown in a) LC-HRMS method for measurement of mitragynine, speciogynine, speciociliatine, and mitraciliatine. The same MS/MS ion transitions in positive mode (*m/z* 399.2278 - > 174.0914, 226.1438, and 238.1436) were used to confirm the peak identity of all diastereomers in both calibrators and patient urine samples (a, inset), whereas quantitative estimation was based on full-scan extracted ion chromatogram mode (*m/z* 399.2278). Chromatograms are shown for (a) a spiked calibrator solution (666 μg/L of each), (b–e) examples of typical patient urine samples containing varying relative amounts of the four diastereomers, and (f) a commercial kratom product (powdered leaves) sold by a Swedish online supplier for the production of soap. [Colour figure can be viewed at wileyonlinelibrary.com]

long time.[25] Using surplus volumes of de-identified routine samples for method development does not require ethical approval.

Some samples had also been tested for the presence of other drugs of abuse with routine methods.[23] Urinary creatinine was determined by the routine Jaffe reaction on a Beckman Coulter DxC 700 AU instrument (quantification limit = 0.3 mmol/L).

2.2 | Routine LC-HRMS multi-analyte method for addictive and herbal drugs in urine

Testing for mitragynine at the Karolinska University Laboratory is part of a validated and accredited LC-HRMS multi-analyte method currently covering 18 less common drugs of abuse and plant-derived substances. The method uses dilution of urine with deuterated internal standards and injection of 2 µl, as described in detail elsewhere.[26] However, with this method, the retention times for mitragynine, speciogynine, and speciociliatine were found to largely overlap, whereas only mitraciliatine was separated (data not shown). It was therefore necessary to modify the chromatographic system to enable individual measurement of the diastereomers.

2.3 | Improved chromatographic system for mitragynine diastereomers

Chromatographic separation of mitragynine, mitraciliatine, speciogynine, and speciociliatine was achieved by methanol gradient elution on a Triart C18 hybrid silica-based column (100 × 2.0 mm I.D., particle size 1.9 µm, pore size 12 nm; YMC, Devens, MA, USA) kept at 60°C. The flow rate was 0.50 ml/min, and the injected sample volume was 2 µl. Mobile phase A consisted of 10 mmol/l ammonium formate and 0.005% formic acid in water (pH 4.8), and mobile phase B was the same buffer but in methanol. The gradient was run as follows: 15% B from 0 to 0.50 min, 15–50% B from 0.50 to 1.00 min, 50–53% B from 1.00 to 2.95 min, 53–95% B from 2.95 to 3.50 min, 95% B from 3.50 to 3.80 min, and then back to 15% B from 3.80 to 4.70 min (Figure 2a).

The LC-HRMS system was a Dionex UltiMate 3000 HPLC and a Q Exactive Orbitrap HRMS (Thermo Fisher Scientific) operated in positive mode, as described for the routine method.[26] The same HRMS/MS ion transitions (*m/z* 399.2278 - > 174.0914, 226.1438, and 238.1436) were used to confirm the peak identity of all four diastereomers, both in calibrators, prepared by spiking drug-negative urine samples with the reference materials, and in patient urine samples (Figure 2a, inset). Acceptance criteria for a positive identification were ± 3 ppm with reference to the theoretical (exact) mass, Gaussian peak shape of analytes, and an absolute relative retention time versus calibrator within ± 0.03 min.

Measurement of the four mitragynine diastereomers in patient urine samples was done in full-scan extracted ion chromatogram mode,[26] by comparison with the urine calibrators for mitragynine, speciogynine, speciociliatine, and mitraciliatine. The quantification limit was 1 µg/L (S/N > 10) for all diastereomers, and the method generated linear results (R > 0.999) up to at least 2000 µg/L.

3 | RESULTS

The improved LC-HRMS method allowed baseline separation of mitragynine (retention time ~3.4 min), speciogynine (~3.6 min), speciociliatine (~3.7 min), and mitraciliatine (~4.0 min), and individual measurement with a total analysis time of less than 5 min (Figure 2a). All 29 patient urine samples testing positive for mitragynine (>100 µg/L) with the routine method were confirmed by the improved separation method to contain mitragynine, but always also the other three diastereomers. Typical examples of chromatograms of patient urine samples are shown in Figure 2b–e. In addition, analysis of a kratom product (powdered plant material) marketed in Sweden for the production of soap revealed that it too contained all four diastereomers with mitragynine showing the highest amount (Figure 2f).

The relative proportions of the diastereomers in the 29 patient urine samples were highly variable. Speciociliatine dominated in most samples (66%), whereas mitragynine and mitraciliatine were highest in 17% each. Overall, mitragynine accounted for 5.5%–53% (range; mean 20%; median 16%), mitraciliatine 18%–56% (32%; 30%), speciogynine 2.0%–13% (6.7%; 5.7%), and speciociliatine 4.6%–69% (41%; 40%) of the total amount (Figure 3). The urine levels of the four diastereomers, expressed both as absolute amounts and relative to the creatinine content, to compensate for differences in urine dilution, are shown in Table 1.

Overall, the urine diastereomer levels showed significant positive correlations with each other (R > 0.93, *P* < 0.0001) (Table S1). However, except for mitragynine and speciogynine for which also the relative amounts were positively correlated, the relative amounts of the other diastereomer showed negative associations.

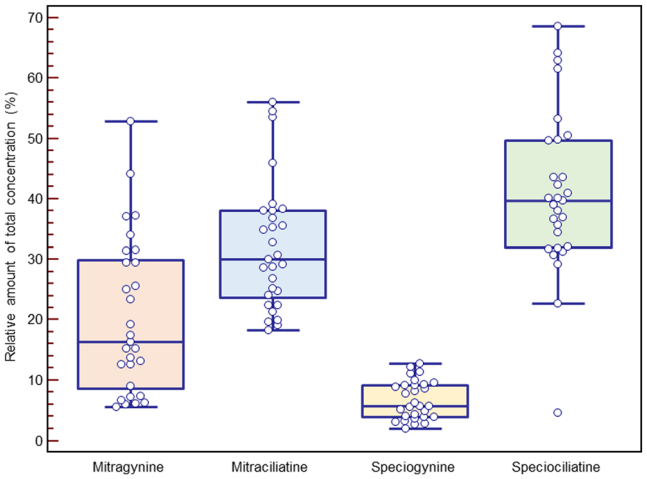

FIGURE 3 Relative amounts of the four mitragynine diastereomers in 29 consecutive patient urine samples submitted for routine drug testing. In most cases (66%), the highest concentration was observed for speciociliatine, whereas mitragynine and mitraciliatine accounted for the highest amount in 17% each. [Colour figure can be viewed at wileyonlinelibrary.com]

TABLE 1 Measured levels of mitragynine and its diastereomers in 29 patient urine samples submitted for routine drug testing

	Concentration (μg/L)			Concentration (μg/mmol creatinine)		
Substance	Range	Mean	Median	Range	Mean	Median
Mitragynine	11–10,079	2209	415	0.5–774	168	57
Mitraciliatine	55–12,039	2433	622	4.9–509	186	126
Speciogynine	4.0–3,700	766	150	0.2–277	58	19
Speciociliatine	19–14,332	3086	802	0.9–711	248	223

4 | DISCUSSION

The high mass resolution offered by the Orbitrap HRMS technique employed in this study provides accurate qualitative analytical information. Nevertheless, because mitragynine and its three diastereomers have identical exact mass and MS/MS transitions, they must be chromatographically separated to enable individual identification and quantification, which has been demonstrated for all diastereomers in only a few previous studies.[24,27] In the present study, this was achieved within 5 min with an improved chromatographic separation method, whereas in the routine multi-analyte method, mitragynine, speciogynine, and speciociliatine were indistinguishable and together formed a merged peak. The new method can be used as a qualitative confirmation method for follow-up analysis of urine samples testing positive for "mitragynine" with the routine method.

All 29 patient urine samples that had tested positive for mitragynine by the routine method were confirmed by the improved separation method to contain mitragynine, which is the only classified substance of the four diastereomers in Sweden. However, in eight samples (28% of cases), the mitragynine level was indicated to be lower than the 100 μg/L routine cutoff (range 11–78 μg/L). Accordingly, as all samples were demonstrated to contain all four diastereomers, the presence of the co-eluting speciogynine and speciociliatine was the reason they had tested positive for mitragynine in the routine analysis. It should be pointed out that there is no nationally agreed cutoff limit for mitragynine.

The presence of all four mitragynine diastereomers in all patient urine samples indicated that they originated from the intake of kratom (i.e., plant material) rather than pure substances. The varying diastereomer ratios agrees with reports that the alkaloid content in the leaves of *Mitragyna* species differs considerably between plant strains, young and old leaves of the same location, geographical and climate conditions, and preparations of kratom products.[27–30] For example, the alkaloid fraction of mitragynine has been reported to vary from about 66% in Thai to only 12% in Malaysian strains. The present observation of negative relative associations between diastereomers, that is, one increases at the expense of another and vice versa, indicated there are different stereochemical metabolic routes in the plants.

At the laboratory, at least 80% of all patient samples testing positive for mitragynine (kratom use) in recent years have originated from drug dependence and psychiatric treatment units, indicating a relation to its opioid and/or stimulant properties.[9] In addition to mitragynine, other psychoactive substances had sometimes been tested for (35%–42% of a total of 92 mitragynine-positive samples since 2020) and encountered, the most common being amphetamines (amphetamine or MDMA; found in ~36% of cases), benzodiazepines (~29%), and cannabis (~21%), showing that kratom was only one of many substances these patients were using. However, it should be noted that most samples were not tested for the full panel of drug substances.

There are several sources of information to indicate that the use of kratom has increased in Sweden. At the Karolinska University laboratory, the frequency of positive samples increased from ≤0.2% in 2016–2018 to 0.5%–0.7% in 2019–2022. Likewise, the number of consultations about kratom poisonings to the Swedish Poisons Information Centre has tripled in recent years (Johanna Grass, personal information), and the Swedish customs seizures of kratom more than doubled (by weight) from 2016 to 2018 (Jenny Åberg, personal information). This highlights an increasing risk for adverse drug events associated with kratom use, including intoxication, addiction, and withdrawal symptoms.[9] Furthermore, there are indications that kratom products have contained artificially elevated concentrations of the potent metabolite 7-hydroxymitragynine.[31] As some samples submitted for mitragynine testing in this study originated from maternity units, it should also be noted that there have been cases with neonatal abstinence syndrome among infants born to mothers who used kratom during pregnancy.[32]

5 | CONCLUSION

There are analytical challenges associated with the detection of kratom use, as routine methods may focus solely on mitragynine and the other three diastereomers are not covered or indistinguishable.[25] The present results revealed that speciociliatine, rather than mitragynine, occurred in the highest amount in most patient urine samples, but its identification required the development of an improved chromatographic separation method. Given the indications of an increased use of kratom in society, and associated public health risks due to addiction problems, serious adverse reactions, and even death, it is important that there are accurate analytical methods that cover all diastereomers. In Sweden, this is also important from a law

enforcement perspective, as only mitragynine is a classified substance while the other three diastereomers, and kratom (plant material), are not. To facilitate legal prosecution, it would have been an advantage if all four diastereomers had been treated equally.

ACKNOWLEDGEMENTS

The authors are indebted to Dr. Torsten Arndt (Germany) for providing the reference material of mitraciliatine.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Anders Helander https://orcid.org/0000-0001-7480-8078

REFERENCES

1. Brown PN, Lund JA, Murch SJ. A botanical, phytochemical and ethnomedicinal review of the genus *Mitragyna* Korth: implications for products sold as kratom. *J Ethnopharmacol*. 2017;202:302-325. doi:10.1016/j.jep.2017.03.020
2. Takayama H, Ishikawa H, Kurihara M, et al. Studies on the synthesis and opioid agonistic activities of mitragynine-related indole alkaloids: discovery of opioid agonists structurally different from other opioid ligands. *J Med Chem*. 2002;45(9):1949-1956. doi:10.1021/jm010576e
3. Basiliere S, Kerrigan S. Identification of metabolites and potential biomarkers of kratom in urine. *J Chromatogr B Analyt Technol Biomed Life Sci*. 2020;1140:121971. doi:10.1016/j.jchromb.2020.121971
4. Babu KM, McCurdy CR, Boyer EW. Opioid receptors and legal highs: *Salvia divinorum* and kratom. *Clin Toxicol (Phila)*. 2008;46(2):146-152. doi:10.1080/15563650701241795
5. Boyer EW, Babu KM, Adkins JE, McCurdy CR, Halpern JH. Self-treatment of opioid withdrawal using kratom (*Mitragyna speciosa* Korth). *Addiction*. 2008;103(6):1048-1050. doi:10.1111/j.1360-0443.2008.02209.x
6. Karunakaran T, Ngew KZ, Zailan AAD, Mian Jong VY, Abu Bakar MH. The chemical and pharmacological properties of mitragynine and its diastereomers: an insight review. *Front Pharmacol*. 2022;13:805986. doi:10.3389/fphar.2022.805986
7. Hartley C 2nd, Bulloch M, Penzak SR. Clinical pharmacology of the dietary supplement kratom (*Mitragyna speciosa*). *J Clin Pharmacol*. 2022;62(5):577-593. doi:10.1002/jcph.2001
8. Henningfield JE, Wang DW, Huestis MA. Kratom abuse potential 2021: an updated eight factor analysis. *Front Pharmacol*. 2021;12:775073. doi:10.3389/fphar.2021.775073
9. Larsen I, Zhang E, Farahmand P. Current understanding of the effects and potential clinical utility of kratom: a review. *J Psychiatr Pract*. 2022;28(2):92-97. doi:10.1097/PRA.0000000000000609
10. Prevete E, Kuypers KPC, Theunissen EL, Corazza O, Bersani G, Ramaekers JG. A systematic review of (pre)clinical studies on the therapeutic potential and safety profile of kratom in humans. *Hum Psychopharmacol*. 2022;37(1):e2805. doi:10.1002/hup.2805
11. Anwar M, Law R, Schier J. Notes from the field: kratom (*Mitragyna speciosa*) exposures reported to poison centers - United States, 2010-2015. *MMWR Morb Mort Wkly Rep*. 2016;65(29):748-749. doi:10.15585/mmwr.mm6529a4
12. Prozialeck WC, Lamar PC, Krupp M 2nd, Moon M, Phelps LE, Grundmann O. Kratom use within the context of the evolving opioid crisis and the COVID-19 pandemic in the United States. *Front Pharmacol*. 2021;12:729220. doi:10.3389/fphar.2021.729220
13. León F, Obeng S, Mottinelli M, et al. Activity of Mitragyna speciosa ("kratom") alkaloids at serotonin receptors. *J Med Chem*. 2021;64(18):13510-13523. doi:10.1021/acs.jmedchem.1c00726
14. Prozialeck WC, Avery BA, Boyer EW, et al. Kratom policy: the challenge of balancing therapeutic potential with public safety. *Int J Drug Policy*. 2019;70:70-77. doi:10.1016/j.drugpo.2019.05.003
15. Halim SA, Low JH, Chee YC, Alias MR. Seizures among young adults consuming kratom beverages in Malaysia: a case series. *Epilepsy Behav*. 2021;121(Pt A):108057. doi:10.1016/j.yebeh.2021.108057
16. Leong Bin Abdullah MFI, Singh D. The adverse cardiovascular effects and cardiotoxicity of kratom (*Mitragyna speciosa* Korth.): a comprehensive review. *Front Pharmacol*. 2021;12:726003. doi:10.3389/fphar.2021.726003
17. Ahmad J, Odin JA, Hayashi PH, et al. Liver injury associated with kratom, a popular opioid-like product: experience from the U.S. drug induced liver injury network and a review of the literature. *Drug Alcohol Depend*. 2021;218:108426. doi:10.1016/j.drugalcdep.2020.108426
18. Schimmel J, Dart RC. Kratom (*Mitragyna speciosa*) liver injury: a comprehensive review. *Drugs*. 2020;80(3):263-283. doi:10.1007/s40265-019-01242-6
19. Olsen EO, O'Donnell J, Mattson CL, Schier JG, Wilson N. Notes from the field: unintentional drug overdose deaths with kratom detected - 27 states, July 2016-December 2017. *MMWR Morb Mortal Wkly Rep*. 2019;68(14):326-327. doi:10.15585/mmwr.mm6814a2
20. Behonick GS, Vu C, Czarnecki L, el-Ters M, Shanks KG. Two single-drug fatal intoxications by mitragynine. *J Anal Toxicol*. 2022;46(5):e110-e114. doi:10.1093/jat/bkac016
21. Schmitt J, Bingham K, Knight LD. Kratom-associated fatalities in northern Nevada - what mitragynine level is fatal? *Am J Forens Med Pathol*. 2021;42(4):341-349. doi:10.1097/PAF.0000000000000695
22. EMCDDA. Kratom drug profile. https://www.emcdda.europa.eu/publications/drug-profiles/kratom_en#control
23. Helander A, Bäckberg M, Beck O. Drug trends and harm related to new psychoactive substances (NPS) in Sweden from 2010 to 2016: experiences from the STRIDA project. *PLoS ONE*. 2020;15(4):e0232038. doi:10.1371/journal.pone.0232038
24. Arndt T, Claussen U, Güssregen B, et al. Kratom alkaloids and O-desmethyltramadol in urine of a "krypton" herbal mixture consumer. *Forensic Sci Int*. 2011;208(1-3):47-52. doi:10.1016/j.forsciint.2010.10.025
25. Papsun DM, Chan-Hosokawa A, Friederich L, Brower J, Graf K, Logan B. The trouble with kratom: analytical and interpretative issues involving mitragynine. *J Anal Toxicol*. 2019;43(8):615-629. doi:10.1093/jat/bkz064
26. Stephanson NN, Signell P, Helander A, Beck O. Use of LC-HRMS in full scan-XIC mode for multi-analyte urine drug testing - a step towards a 'black-box' solution? *J Mass Spectrom*. 2017;52(8):497-506. doi:10.1002/jms.3946
27. Manwill PK, Flores-Bocanegra L, Khin M, et al. Kratom (*Mitragyna speciosa*) validation: quantitative analysis of indole and oxindole alkaloids reveals chemotypes of plants and products. *Planta Med*. 2022;88(9-10):838-857. doi:10.1055/a-1795-5876
28. Boffa L, Ghè C, Barge A, Muccioli G, Cravotto G. Alkaloid profiles and activity in different *Mitragyna speciosa* strains. *Nat Prod Commun*. 2018;13(9):1934578X1801300904. doi:10.1177/1934578X1801300904
29. Shellard EJ, Lala PK. The alkaloids of *Mitragyna rubrostipulata* (Schum.) Havil. *Planta Med*. 1978;33(01):63-69. doi:10.1055/s-0028-1097360
30. Philipp AA, Wissenbach DK, Weber AA, Zapp J, Maurer HH. Metabolism studies of the kratom alkaloids mitraciliatine and isopaynantheine, diastereomers of the main alkaloids mitragynine and paynantheine, in rat and human urine using liquid chromatography-linear ion trap-mass spectrometry. *J Chromatogr B Analyt Technol*

Biomed Life Sci. 2011;879(15-16):1049-1055. doi:10.1016/j.jchromb.2011.03.005

31. Lydecker AG, Sharma A, McCurdy CR, Avery BA, Babu KM, Boyer EW. Suspected adulteration of commercial kratom products with 7-hydroxymitragynine. *J Med Toxicol*. 2016;12(4):341-349. doi:10.1007/s13181-016-0588-y
32. Wright ME, Ginsberg C, Parkison AM, Dubose M, Sherbondy M, Shores E. Outcomes of mothers and newborns to prenatal exposure to kratom: a systematic review. *J Perinatol*. 2021;41(6):1236-1243. doi:10.1038/s41372-021-00952-8

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Helander A, Rylski A. Drug testing for mitragynine and kratom: Analytical challenges and medico-legal considerations. *Drug Test Anal*. 2023;15(2):213-219. doi:10.1002/dta.3391